REMARKS

Claims 23 to 44 are pending in the application.

Lack of Unity of Invention

The examiner states that the application contains three groups of invention that are not so linked as to form a single general inventive concept under PCT Rule 13.1.

The examiner requests that applicant elect a single invention from the groups I, II and III as defined in the office action - election has been made with traverse.

In examiner's opinion the groups lack a general inventive concept because they lack a special technical feature. The examiner points out that there are **three** inventions, the first being a product and the second and third being methods of producing the product. As pointed out by the examiner, 37 CFR 1.475 provides for a category for a single product; a single method of making the product, and a single method of using the product. The examiner then states that inventions II and III are drawn to different methods of making a product and that the methods are different because of the non-overlapping pH conditions.

It is respectfully submitted that the invention III - claims 41-44 - is directed to a method of USING the product of claim 23 and not a method of MAKING the product of claim 23. Note that the product of claim 23 is used as a substrate. In other words, claim 41 is directed to using the metallic object according to claim 23 for immobilizing complementary nucleic acid compounds selected from the group consisting of nucleic acids and nucleic acid derivatives. Note that in the method step of selecting a pH value and an ion strength the metal oxide layer of the metallic object and the nucleic acid compounds of the coating of the metallic object are referenced. The product made by claim 23 is being USED in the claims 41-44 and not made by the process of claims 41-44.

Therefore, as a product and a method of using the product pursuant to 37 CFR 1.475(b)(2) **"will be considered to have unity of invention",** the claims 41-44 must be rejoined as the special technical feature resides in the product itself.

As regards the special technical feature lacking in the product (invention I) and the method of making the product (invention II), it is respectfully submitted that the prior art *Bitner* does not show STABLE and IRREVERSIBLE INCORPORATION of the terminal molecular areas in the metal oxide layer; incorporation is not shown in *Bitner* - only sorption to the substrate surface which is reversible. In order to clarify "incorporation" in the metal

oxide layer, the claims have been amended to define that a metal oxide layer is grown about the 5'-terminal or 3'-terminal molecule area and the 5'-terminal or 3'-terminal molecule areas are embedded in the metal oxide layer.

The invention II (claims 37-40) are therefore to be rejoined as well.

WIPO Document

The examiner stated in the last office action that applicant referred to a WIPO document but that the application file, including the most recent office action, does not refer to any WIPO documents; examiner requested clarification.

The discussed reference WO 92/18514 has been cited by the examiner in the office action dated 7/3/2007 on page 2, 2nd paragraph, last sentence: "*In the instant case the product of Group I can be made by a materially different process, such as that which is disclosed by WO 92/18514.*"

Claim Rejections - 35 U.S.C. 112

Claims 24 and 26 stand rejected under 35 U.S.C. 112, 2nd paragraph, as being indefinite.

In claim 24, the wording "to a large extent" has been deleted.

In claim 26, "groups" has been changed to "group".

Rejection under 35 U.S.C. 102

Claims 23-30, 32, 33, 35, 36 stand rejected under 35 U.S.C. 102(b) as being anticipated by *Bitner (EP 0 391 608).*

The examiner argues that *Bitner* anticipates claim 23 because the reference discloses a solid support comprising an amount of metal oxide with a coating that is comprised of a thin metal oxide layer as disclosed on page 3, line 20; page 4, line 16; page 7, lines 15-16; and nucleic acid molecules having their 5'-terminal or 3'-terminal ends incorporated into the metal oxide layer as disclosed on page 3, lines 22-23.

Applicant respectfully disagrees. First of all, there is no mention whatsoever in the entire reference relating to the 5'-terminal or 3'-terminal ends being incorporated into the metal oxide layer or coating. The 5'-terminal or 3'-terminal ends of the nucleic acids are never mentioned. The only disclosure to be found at page 3, lines 22-23 (it appears that examiner meant to refer to lines 21-22) is that:

"(b) nucleic acids sorbed to at least a portion of the available surface of the support

in a manner such that the nucleic acid substantially retains biological accessibility and reactivity.".

Nothing is said about how the nucleic acid is sorbed or which part of the nucleic acid sorbs to the surface in this text portion. The only feature mentioned is that the nucleic acid retains biological accessibility and reactivity, i.e, hybridization.

However, the hybridization capability allows no conclusion whether the nucleic acid is sorbed to the surface of the metal oxide by the 5'-terminal or 3'-terminal ends or by its backbone; immobilization of the nucleic acid by way of the backbone is generally sufficient for enabling hybridization.

Moreover, *Bitner* discloses that the phosphate groups of the DNA backbone may play a significant role in the sorption of the nucleic acids to the metal oxide (page 5, lines 32-33), i.e., in *Bitner* it is not the 5'-terminal or 3'-terminal end but the backbone sorbing to the metal oxide.

This is a significant difference to the present invention as pursuant to the present invention the nucleic acid molecules bind by means of the 5'-terminal or 3'-terminal anionic group to the metal oxide. In this way, in contrast to the sorption by means of the backbone, there is a substantially unhindered steric accessibility, especially a free movability of the remaining nucleic acid strand required for forming three-dimensional structures.

The present invention provides a regio-selective incorporation of the nucleic acids by means of the 5'-terminal or 3'-terminal ends and, in this way, the unincorporated sections are freely movable. This makes them accessible for the hybridization reactions and also for biological processes in which the secondary and tertiary structures of the nucleic acids are important. See particularly page 4, 2nd to 4th full paragraphs, of the instant specification.

Applicant submits three publications A1, A2, A3 of the inventors (published after the filing of the international application of which the instant application is a national stage filing) as evidence that the present invention, in addition to maintaining the hybridization capability, also enables the immobilization of the nucleic acid aptamers while maintaining the biological activity; see especially paragraph 2.6. of publication A3 (A1 and A2 describe the inventive method per se).

An aptamer is a short DNA or RNA single strand (40 to 80 bases) that is capable

of specifically binding molecules by means of its three-dimensional structure. A3 deals with aptamers binding specifically to osteoblasts. For bonding to occur the nucleic acid aptamer must be freely moveable and able to form its secondary and tertiary structures. By means of the present invention, a structural and functional retention is provided that goes far beyond the hybridization capability. This is evidenced by the functionality of the aptamers fixed on the substrate by means of the method according to the invention which aptamers retain their specificity for binding special cell populations even after immobilization on Ti/Ti alloy (see A3).

A3 is proof positive of the regio specificity in regard to immobilization of the nucleic acids achieved with the present invention. Only a freely movable (i.e., not even partially bonded by the backbone to the substrate surface) DNA single strand is capable - after immobilization - of forming the defined three-dimensional structure required for realizing the aptamer functionality.

In particular applicant would also like to point out that the gist of the invention is that the 5'-terminal or 3'-terminal ends are "incorporated" or, as now more specifically defined in the claims, are embedded in the metal oxide layer that is grown about the 5'-terminal or 3'-terminal molecule areas; see in particular Fig. 2 where the incorporation or embedding in the metal oxide is shown). The 5'-terminal or 3'-terminal molecule areas are not merely sorbed to the surface but are embedded in the growing metal oxide layer (see page 4, 1st full paragraph). The nucleic acids are fixed in the metal oxide and cannot be removed; the sorbed nucleic acids of *Bitner* however can be desorbed (see page 8, lines 42-46, where the desorption of the nucleic acids is described as an important attribute of the disclosed composition) and there is no teaching in regard to embedding the sorbed portions.

Claim 23 is therefore neither anticipated nor obvious in view of *Bitner* and should be allowable together with its dependent claims.

Reconsideration and withdrawal of the rejection of the claims under 35 USC 102 are therefore respectfully requested.

Rejection under 35 U.S.C. 103

Claim 31 stands rejected under 35 U.S.C. 103(a) as being unpatentable over *Bitner* in view of *Wengel et al. (US 6,670,461).*

Claim 34 stands rejected under 35 U.S.C. 103(a) as being unpatentable over *Bitner*

in view of *Yabusaki et al. (WO 85/02628).*

Claim 23 is believed to be allowable; its dependent claims should be allowable also.

CONCLUSION

In view of the foregoing, it is submitted that this application is now in condition for allowance and such allowance is respectfully solicited.

Should the Examiner have any further objections or suggestions, the undersigned would appreciate a phone call or **e-mail** from the examiner to discuss appropriate amendments to place the application into condition for allowance.

Recognizing that Internet communications are not secure, I hereby authorize the USPTO to communicate with me concerning any subject matter of this application by electronic mail. I understand that a copy of these communications will be made of record in the application file.

Authorization is herewith given to charge any fees or any shortages in any fees required during prosecution of this application and not paid by other means to Patent and Trademark Office deposit account 50-1199.

Respectfully submitted on November 28, 2007,

/Gudrun E. Huckett/

Ms. Gudrun E. Huckett, Ph.D.
Patent Agent, Registration No. 35,747
Schubertstr. 15a
42289 Wuppertal
GERMANY
Telephone: +49-202-257-0371
Facsimile: +49-202-257-0372
gudrun.draudt@t-online.de

GEH

Enclosures:

A1: D. Scharnweber et al.: Designing Metallic Biomaterial Surfaces by Anionic Immobilization of DNA Single Strands Utilizing Hybridization for Attachment of Biomolecules; European cells and Materials 2004, Vol. 7, page 85

A2: J. Michael et al.: Surface Modification of Titanium-Based Alloys With Bioactive Molecules Using Electrochemically Fixed Nucleic Acids; J. Biomed. Mater. Res. B 80 (2007) 146-155

A3: K.T. Guo.: The effect of electrochemical functionalization of Ti-alloy surfaces by aptamer-based capture molecules on cell adhesion; Biomaterials 28 (2007) 468-474